

CDMRP 
Department of Defense

Prostate Cancer Research Program



U.S. Army Medical Research and Materiel Command



Congressionally Directed Medical Research Programs



The Office of the Congressionally Directed Medical Research Programs (CDMRP) was created in 1992 from a powerful grassroots effort led by the breast cancer advocacy community that resulted in a congressional appropriation of funds for breast cancer research. This initiated a unique partnership among the public, Congress, and the military. Since then, the CDMRP has grown to encompass multiple targeted programs and has received nearly \$7 billion (B) in appropriations from its inception through fiscal year 2012 (FY12). Funds for the CDMRP are added to the Department of Defense (DoD) budget, in which support for individual programs, such as the Prostate Cancer Research Program (PCRP), is allocated via specific guidance from Congress.

APPLICATION REVIEW PROCESS

The CDMRP uses a two-tier review process for application evaluation, with both tiers involving dynamic interaction among scientists and disease survivors. The first tier of evaluation is a scientific peer review of applications measured against established criteria for determining scientific merit. The second tier is a programmatic review conducted by the Integration Panel, which is composed of leading scientists, clinicians, and consumer advocates. The Integration Panel compares applications to each other and makes recommendations for funding based on scientific merit, portfolio balance, and relevance to program goals.

Prostate Cancer Research Program Background and History

Since its inception in 1997 and over its 15-year history of congressional support totaling \$1.2B, the DoD PCRP has changed the landscape of biomedical research, energizing the research community to conduct high-risk research that is optimally collaborative, innovative, and impactful on prostate cancer. The PCRP has played a major role in supporting the development of new treatments for advanced prostate cancer, has been the leading supporter of research toward understanding and resolving ethnic disparities in prostate cancer incidence and mortality, and has fostered the development of hundreds of new investigators who have become leaders in cutting-edge research that is making a difference for hundreds of thousands of prostate cancer patients and will ultimately conquer the disease.

VISION

Conquer prostate cancer

MISSION

Fund research that will lead to the elimination of death from prostate cancer and enhance the well-being of men experiencing the impact of the disease

Integration Panel

The eighteen members of the PCRP Integration Panel represent some of the nation's foremost innovative minds and creative leaders in academia, the private and non-profit sectors, and advocacy. These scientists, clinicians, and consumer advocates bring many years of experience to bear – in basic, translational, and clinical research – on the singular goal of conquering prostate cancer. Together, members of the panel synergize their expertise and pioneering vision to outline a coherent and cohesive investment strategy that has set the program on a trajectory to eliminate death and suffering from prostate cancer through development of new therapies, diagnostics, and technologies while encouraging new discoveries for even greater impact on the disease.



"The PCRP is a highly respected and sought-after funding mechanism. It is critical for the discovery and development of new preventative, diagnostic, and therapeutic modalities that will directly lead to improving the lives of prostate cancer patients and their families. It has provided an outstanding and visionary platform and investment both in unique and transformative science and the next generation of scientists that will bring us closer to our overarching objective of reducing death and suffering and ultimately eliminating prostate cancer.

As a physician who is directly involved in the care of prostate cancer patients, it is my honor to serve on the PCRP Integration Panel, and it is a privilege to work with such a dedicated team of advocates, researchers, program members, and administrators and be able to contribute to this noble cause."

Maha Hussain, M.D., F.A.C.P.
FY13 PCRP Integration Panel Chair
Professor of Medicine and Urology; Associate Director for Clinical Research;
Co-Leader, Prostate Cancer Program; University of Michigan
Comprehensive Cancer Center; Associate Chief for Clinical Research;
Division of Hematology/Oncology, Department of Internal Medicine



"Do we want to cure cancer? I often ask this question in those moments when it seems our national will to fight this dreaded disease is waning. However, the one constant in the struggle to cure prostate cancer has been the Prostate Cancer Research Program through the Department of Defense. Despite sequestration threats, budget cutbacks, and legislative wrangling, the PCRP has remained committed to the cause by ensuring the best possible research is funded to eliminate the death and suffering from prostate cancer. Many of the recently approved agents for advanced stage prostate cancer have been the direct result of research supported by the PCRP. We cannot let this vital resource go fallow, and it's of great

value to me that I can contribute as an advocate for research funded through this program. The future health of our country and the Constitutional promise of life, liberty, and the pursuit of happiness are integrally tied into finding a cure for this disease, which kills more than 30,000 men a year and compromises the economic health of our society."

Virgil Simons, M.P.A.
FY12 PCRP Integration Panel Chair
Founder and President, The Prostate Net

Integration Panel Members

Maha Hussain, M.D., F.A.C.P.
FY13 Chair
University of Michigan

Virgil Simons, M.P.A.
FY12 Chair
The Prostate Net

Philip Arlen, M.D.
Neogenix Oncology, Inc.

James Brooks, M.D.
Stanford University School of Medicine

Alvin Chin, J.D.
Virginia Prostate Cancer Coalition

Robert Gillies, Ph.D.
Moffitt Cancer Center

James Kiefert, Ed.D.
Us TOO International

Deborah Kuban, M.D., F.A.C.R., F.A.S.T.R.O.
University of Texas M. D. Anderson Cancer Center

Natasha Kyprianou, Ph.D.
University of Kentucky

Timothy McDonnell, M.D., Ph.D.
University of Texas M. D. Anderson Cancer Center

Peter Nelson, M.D.
Fred Hutchinson Cancer Research Center

Elizabeth Platz, Sc.D., M.P.H.
Johns Hopkins Bloomberg School of Public Health

Victor Reuter, M.D.
Memorial Sloan-Kettering Cancer Center

A. Oliver Sartor, M.D.
Tulane University School of Medicine

Westley Sholes, M.P.A.
California Prostate Cancer Coalition

Howard Soule, Ph.D.
Prostate Cancer Foundation

Donald Tindall, Ph.D.
Mayo Clinic, Rochester

Spurring the Prostate Cancer Research Focus for a Cure:

PCRP OVERARCHING CHALLENGES

The PCRP is partnering with the most innovative minds in prostate cancer to overcome the greatest challenges facing clinicians while ensuring that critical needs for prostate cancer patients are being addressed by PCRP-funded research. Toward that end, all applicants are encouraged to target their research efforts in one of three key areas:

- ***Develop better tools to detect clinically relevant disease in asymptomatic men***
- ***Distinguish aggressive from indolent disease in men newly diagnosed with prostate cancer***
- ***Develop effective treatments and address mechanisms of resistance for men with high risk or metastatic prostate cancer***

These three overarching challenges are consistent with the program's overall goals and place a demand on investigators to push the boundaries of discovery, improve methods for decision making and develop new therapeutic approaches for prostate cancer management.

PCRP Overall Goals

- Support highly innovative, groundbreaking research;
- Support high-impact research with near-term clinical relevance;
- Sponsor multidisciplinary synergistic research;
- Fund translational studies to support the fluid transfer of knowledge between bedside and bench;
- Invest in research on patient survivorship and quality of life;
- Foster the next generation of prostate cancer investigators through mentored research;
- Promote research on disparities in the incidence and mortality of prostate cancer



"The PCRP and its advisory integration panel members recognize the fact that a significant number of men are over-treated for prostate cancer each year. Some of these men suffer extensive side effects from treatment that can impair the patient's quality of life and in turn impose a significant burden on health care resources. This underscores the urgency to distinguish aggressive from indolent prostate cancer. The PCRP's challenge to the prostate cancer research community is to focus research efforts using all the genetic, molecular, biochemical, and radiologic tools available to identify phenotypes/biomarkers that are prognostic indicators of prostate cancer progression and lethality that, when analyzed by genetic, functional, or translational studies, can be qualified to predict aggressive versus indolent disease. The diagnostic and prognostic value of these markers would be tremendous as they hold significant promise in guiding treatment decisions for men with prostate cancer. Improving the clinical management of prostate cancer in patients is an issue of critical importance for the PCRP, and I am pleased to be part of the effort shaping the vision — of conquering prostate cancer — by supporting this overarching challenge."

Elizabeth A. Platz, Sc.D., M.P.H.

*Professor and Martin D. Abeloff, M.D. Scholar in Cancer Prevention, Cancer Epidemiology Area of Concentration,
Department of Epidemiology, Johns Hopkins University Bloomberg School of Public Health
FY13 PCRP Integration Panel Member*

search Community to

PCRP FOCUS AREAS

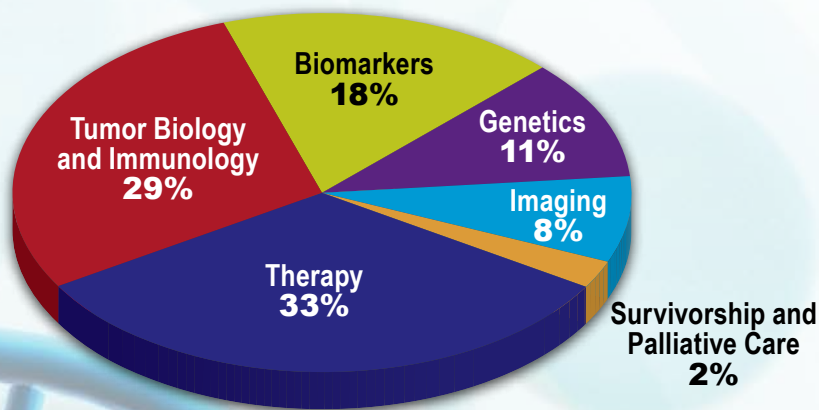
The PCRP established seven focus areas to assist researchers in focusing their projects around program priorities. The focus areas also serve as a mechanism for the program to track whether the PCRP portfolio of funded awards is best aligned with those areas of research that are in greatest need of advancement. The pie chart below shows the number of awards funded in each of the PCRP focus areas since they were introduced in FY09. Thirty-three percent of the portfolio is focused on therapy, 29% on tumor biology and immunology, 18% on biomarkers, 11% on genetics, 8% on imaging, and 2% on survivorship studies. In 2013, the PCRP refined the focus areas to align with the most current needs of the prostate cancer research field.

FY13 Focus Areas:

- ***Biomarker development***
- ***Genetics***
- ***Imaging***
- ***Mechanisms of resistance***
- ***Survivorship and palliative care***
- ***Therapy***
- ***Tumor and microenvironment biology***

FY09–FY11 PCRP Portfolio by Focus Area*

*Chart shows percentage of awards in each focus area using the primary area of each award.



informed decisions for managing their cancer.”

“Over the past 25 years, PSA screening has changed the face of prostate cancer. While the number of men presenting with advanced prostate cancer has dropped dramatically, small, less aggressive cancers are being found that do not require treatment. This fundamental change in prostate cancer detection necessitates a change in how we manage the disease. Of the entities supporting prostate cancer research, the PCRP has led the investment in research to understand the fundamental biology of prostate cancer as it applies to the important clinical question of distinguishing lethal from nonlethal prostate cancer at its earliest stages. With a broad portfolio of research approaches including molecular imaging, genomics, nanotechnology, health outcomes research, and many others, the PCRP drives the discoveries that will help patients and their physicians make the best and most

James D. Brooks, M.D.
Keith and Jan Hurlbut Professor, Stanford University,
Chief of Urologic Oncology, Department of Urology, Stanford University School of Medicine
FY13 PCRP Integration Panel Member

PCRP Consumer Advocates

Integral involvement by consumer advocates (disease survivors) on review panels has helped to shape the direction, goals, and funding recommendations of the PCRP. By sharing their perspective as prostate cancer patients, they have inspired and enlightened investigators and caregivers, encouraging both to seek innovative solutions to the challenges in prostate cancer today. The collective wisdom and partnership between consumer advocates, scientists, and clinicians have forged a new decade of exciting advancements in clinical therapeutics and technology.



"I was diagnosed with prostate cancer at the age of 44 and treated through radical prostatectomy. I am African American and, as such, part of a high-risk group, but I am currently 5 years out from surgery, cancer-free, and in great health. When I started this journey, I didn't know how serious a disease prostate cancer was for men of color – but then I joined that club. The PCRP has given me a wonderful opportunity to be on the inside of prostate cancer research and to have my opinion heard on the viability of the numerous approaches being proposed to treat this silent killer. My hope is that the research being funded, now and in the future, will help to eradicate this disease for all men. I'm honored to be a part of that process."

Richard Satterwhite, Roswell Park Cancer Institute



"As the leader of an Us TOO prostate cancer support group in New Jersey, and a 5-year prostate cancer survivor, I spend a lot of time researching treatment options for myself and others. For the past two years I have participated as a consumer reviewer in the PCRP peer reviews, and this experience has taught me a lot about research and much more. I've gained invaluable insight, but more importantly, I have been able to draw on my experience as a prostate cancer survivor in judging the efficacy of the proposed research and how the result would benefit prostate cancer patients. I serve on a panel with learned scientists and clinicians I would not otherwise have access to, and my evaluations weigh equally with theirs in the review process. Having served in the U.S. Army for four years, I appreciate the efficiency of the CDMRP sponsoring this valuable program for prostate cancer patients around the world."

Robert Sherman, Us TOO International



"As a prostate cancer survivor diagnosed at 48 years of age and a prostate cancer activist, I was humbled to be selected as a consumer reviewer. This is an unparalleled opportunity to provide input on groundbreaking research from a patient's perspective. The entire review process was one of the most rewarding experiences that I can recall – truly a way to give back to the prostate cancer community that has supported me."

John Salata, ZERO: The Project to End Prostate Cancer



"I am a 2-year survivor of prostate cancer. Since my diagnosis in July 2010 at the age of 56, it has been my mission to assist prostate cancer patients with education and awareness. In 2011 and again this year, I participated as a consumer reviewer for the PCRP. The program included many experts and dedicated professionals coming together to find ways to improve the quality of life issues facing prostate cancer patients. It was a privilege to serve on the review panel. Dedicated programs like the PCRP will ensure that prostate cancer awareness remains at the forefront and continues to be on the cutting edge of eradicating prostate cancer.....We will find a cure!"

Thomas Wallace, Sr., American Cancer Society



"My participation as a consumer reviewer in the DoD PCRP was one of the most rewarding experiences of my life. It was rewarding from both a prostate cancer survivor perspective and from a general consumer perspective. It was wonderful to appreciate the consideration and value that scientists give to consumer comments. This provided a balanced grant review approach that I never dreamed to be true and added much value to the review process. In addition, it was a very personal enlightening educational experience for me to gain a deeper understanding of one of many federal government-sponsored efforts in the pursuit of a cure for prostate cancer."

Lewis Bellinger, Us TOO International

PCRP Scientists and Clinicians

Scientists and clinicians serve as peer reviewers to provide expert advice on the scientific and technical merit of research proposals. Together they are tasked with measuring each application against a gold standard for innovation and impact, along with a well-reasoned scientific rationale and research strategy for addressing the hypothesis proposed. This assessment is a critical component in enabling the program to identify innovative, high-risk, high-impact approaches to prostate cancer that will move the field toward accomplishing the PCRP mission of funding research that will eliminate death from prostate cancer and enhance the well-being of men experiencing the impact of the disease.



"In order to be truly translational, researchers always have to consider the ultimate beneficiary of their work. One of the most meaningful aspects of the PCRP has been understanding the views of the prostate cancer community as they relate to research. The advocates, participating as full members of the review committee, focus the discussion in a very important way."

Clifford C. Dacso, M.D., Baylor College of Medicine



"It is a distinct pleasure to serve on the review panels of the PCRP. This program is unparalleled in supporting outside-the-box ideas and highly innovative research proposals aimed at addressing unmet needs in prostate cancer. The unique mix of reviewers – basic scientists, clinical and translational researchers, and consumer advocates – helps identify not only the best science, but also the most relevant and most impactful proposals."

Hari Koul, Ph.D., University of Colorado Comprehensive Cancer Center



"I have been fortunate to be a reviewer for the CDMRP Prostate Cancer Research Program since its inception. As the program has matured, we have seen an increasing number of cutting-edge research projects from investigators over a broad range of sciences. The PCRP has become a linchpin for support of patient-oriented research and especially for research that has focused a bright light on the ravages of prostate cancer in the African American population. Not only is it crucial that this program continue but it must expand if the advances made to this point are to enter into clinical practice. No other funding program has this flexible capability."

Stephen R. Plymate, M.D., University of Washington



"My experience as a peer reviewer was rewarding; it reinforced my sense of the PCRP's tremendous commitment to the many scientists and consumer advocates working collectively in the fight against prostate cancer. This program has made invaluable contributions toward fighting a disease that impacts us all profoundly and weighs significantly on the African American community."

Arthur Burnett, M.D., The James Buchanan Brady Urological Institute at Johns Hopkins



"The PCRP has set an important clinical translation-focused research agenda. It is unique and distinct from other funding organizations. The PCRP has the distinction of supporting seed ideas of individual scientists, an approach that fosters innovation and impact – viable clinical translation needs a good balance between innovation and strong validation of concepts. I treasure the opportunity to interact with consumer reviewers on review panels. Their perspectives always keep me grounded on what we need to achieve in prostate cancer research. I believe strongly that we can achieve victory in this mission within the next decade."

Lily Wu, M.D., Ph.D., University of California, Los Angeles, David Geffen School of Medicine

Supporting Strategic Partnerships and Leveraging for a Breakthrough: PCRP's National Research Resources

THE IMPACT OF INNOVATION AND COLLABORATION ON PROSTATE CANCER CLINICAL TRIALS

It took the Prostate Cancer Clinical Trials Consortium (PCCTC) less than eight years to receive U.S. Food and Drug Administration (FDA) approval for two new drugs — **abiraterone (ZYTIGA®)** and **enzalutamide (XTANDI®)** — a remarkable feat for any clinical trial entity. Both drugs can be taken orally – other drugs used to treat prostate cancer are given intravenously – and are currently being used to treat men with metastatic, castration-resistant prostate cancer and target different mechanisms of androgen receptor (AR) activation, a process that fuels prostate cancer cells to grow and spread. With the approval of these two agents, the PCCTC has contributed significantly to the most **significant advances** in the treatment of metastatic castration-resistant prostate cancer in almost a decade.





Initially begun in 2005 with combined support from the PCRP and the Prostate Cancer Foundation, the PCCTC has expanded from 8 to **13 academic institutions** with a coordinating center at Memorial Sloan-Kettering Cancer Institute under the leadership of Dr. Howard Scher. The PCRP's investment of \$41.3 million to date to accelerate **hypothesis-driven Phase I and II clinical trials** of promising new therapeutic agents and treatment approaches for clinical practice is rapidly changing the clinical trial landscape, **impacting the disease** and the standard of care for men with advanced prostate cancer. Centralized management and streamlined clinical trial development processes allow investigators from all the participating institutions (i.e., clinical sites) to focus on accelerating clinical trials and research efforts by establishing scientific priorities and definitive endpoints that will help produce the most informative data. The consortium is also **at the forefront of the personalized medicine** arena, incorporating biomarker components into trials and implementing a clinical stages model of prostate cancer that helps to ensure that each patient assigned to a study receives the specific type of treatment that provides the **most benefit to that patient**.

To date, the PCCTC has developed **156 clinical trials**, with 79 trials completed and 77 trials still active or pending activation. Remarkably, the PCCTC accounts for the conduct of nearly **25% of all early-phase prostate cancer clinical trials** that are reported on ClinicalTrials.gov. **Over 3,500 patients**, 13% from minority populations, have been enrolled in PCCTC clinical trials of novel therapeutics. **Nine candidate drugs have advanced to Phase III**, and the PCCTC continues to prime the pipeline with promising novel agents that will undergo rapid design, development, and implementation of early-phase clinical trials. PCRP support for clinical research is yielding **significant results for patients**, and it is anticipated that within the first decade of the PCCTC's existence, additional therapeutics will become available to eliminate death and suffering from prostate cancer in men with metastatic, castration-resistant disease. This is just one area in which the PCRP investment in clinical research is **driving innovation and accelerating the vision of conquering prostate cancer**.



PROSTATE CANCER BIOREPOSITORY NETWORK

THE PROSTATE CANCER BIOREPOSITORY NETWORK: A NEW RESOURCE AVAILABLE TO THE PROSTATE CANCER RESEARCH COMMUNITY

The Prostate Cancer Biorepository Network (PCBN) was initiated in 2009 by the PCRP in response to the prostate cancer research community's need for high-quality human prostate cancer biospecimens. The PCRP offered the Prostate Cancer Pathology Resource Network award mechanism with the goal of developing a biorepository consortium to manage the acquisition and distribution of high-quality, well-annotated biospecimens for wide use by prostate cancer investigators. Critical to achieving this goal are optimized and standardized protocols for collecting biospecimens, and an infrastructure to facilitate the growth of the resource.

In collaboration with the DoD, the PCBN currently consists of two participating institutions: the Johns Hopkins School of Medicine, led by Dr. Bruce Trock, and the New York University Medical Center, led by Dr. Jonathan Melamed. The Coordinating Center, located at Johns Hopkins Medical Center, serves as the administrative nexus of the network. The PCBN capitalizes on both the extensive biospecimen availability at these institutions, and the experience in prostate cancer pathology and biomarker



research of its scientists. Another important component of the PCBN is an online bioinformatics infrastructure to facilitate access to the biorepository and maintain inventory; this information can be accessed through the online informatics system, <http://prostatebiorepository.org>. Here, investigators can obtain information about the biorepository and its biospecimens and data, as well as information on governance, policies, standard operating procedures, the process for requesting biospecimens and/or data, application forms, prioritization and review criteria for biospecimen requests, available expertise in biospecimen science, and much more.

In its relatively short history, the PCBN has amassed a sizeable collection of biospecimens, including tissues from biopsies, prostatectomies, and rapid autopsies, as well as body fluids such as serum, plasma, buffy coat, and prostatic fluid. They have also derived DNA and RNA from these samples, and prepared tissue microarrays. Importantly, all biospecimens are linked to clinical and outcome data, and supported by the online informatics system. Prostate cancer investigators can browse the website for available samples, or request that specific samples be prepared. The PCBN has implemented a framework that categorizes the biospecimens into one of three groups to assist investigators in decision making: (1) biospecimens with little or no linked data for early research questions requiring no preliminary data; (2) high-value biospecimens with linked data or other linked biospecimen type (requires preliminary data and functional assays); and (3) rare and/or data-rich biospecimens (requires very mature preliminary data). PCBN scientists will work with the prostate cancer investigators to make sure they are receiving the most appropriate samples for their study. In some cases, PCBN scientists will collaborate with investigators on their project to ensure successful completion of the study.

Additional efforts by the PCBN include the development of new biomarker assays, refinement and development of new protocols for the collection of bone marrow biopsies, and accrual of advanced and metastatic prostate cancer biospecimens.

The rapid development and successful launch of the biorepository are a tribute to the combined expertise, experience, collaborative leadership, and intellectual synergy of the multidisciplinary scientists involved in this effort. The PCBN is now poised to contribute significantly to the validation and qualification of prostate cancer biomarkers for use in clinical management and advancing the understanding of tumor biology toward clinical translation.

High Impact Accomplishments from PCRP-Funded Research



Basic Research

- **Lymphotoxin** – Dr. Michael Karin discovered that castration therapies trigger an inflammatory response involving B-cell derived lymphotoxin that promotes the development of **castration-resistant prostate cancer (CRPC)**. These results suggest lymphotoxin may be an important target for CRPC therapy.
- **SPINK1** – Dr. Arul Chinnaiyan discovered that the gene SPINK1 is overexpressed in 10% of prostate cancers and that these cancers were found in patients with more aggressive disease, potentially identifying an important **subtype of prostate cancer** that may respond well to specific treatments.
- **PHLPP1** – Dr. Lloyd Trotman discovered a new tumor suppressor gene, PHLPP1 (“flip one”) that cooperates with the gene PTEN to prevent prostate cancer **progression to aggressive disease**, providing new insight on therapeutic targeting of this pathway.
- **TMPRSS2-ETS gene fusions** – Dr. Michael Rosenfeld discovered a mechanism involving AR recruitment at the sites of common chromosomal breaks and the induction of structural changes that bring the TMPRSS2 gene in close proximity to ETS family genes, enabling their fusion. TMPRSS2-ETS gene fusions are found in over 50% of patients with prostate cancer and may provide a key to developing **therapeutics and biomarkers**, and offer greater insight into the origins and progression of the disease.

Translational Research

- **PET radiotracers** – Dr. Martin Pomper developed PET radiotracers, specifically targeting prostate cancer cells through the peptide PMSA, that have been patented and are in Phase I clinical trials for enhanced **imaging** of metastatic prostate cancer.
- **DNA vaccine** – Dr. Douglas McNeel developed an **immunotherapy**-based DNA vaccine, now in a Phase II clinical trial, to inhibit prostate cancer recurrence in patients after treatment for primary disease.
- **Anti-N-cadherin monoclonal antibodies** – developed by Drs. Robert Reiter and Matthew Rettig, these **antibodies inhibit prostate cancer growth**, and delay the time to emergence of castration resistance, local invasion and metastasis of CRPC.
- **EPI-001** – a novel small molecule inhibitor developed by Dr. Marianne Sadar, binds to the AR amino terminal region and **blocks the growth of CRPC**. In vitro and in vivo studies showed that EPI-001 abrogated critical protein-protein interactions induced by AR that leads to uncontrolled growth of CRPC cells.
- **Magnetic resonance imaging (MRI)-guided robotic device** for prostate biopsies and brachytherapy – Dr. Gregory Fischer developed a **robotic system for MRI-guided, real-time needle placement** in prostate biopsy sample retrieval and brachytherapy seed placement. This device was demonstrated to be fully functional inside a 3T MRI scanner using phantoms and is now in preclinical development.
- **Custirsen (OGX-011)** – Dr. Kim Chi developed OGX-011, a second-generation antisense molecule that blocks the protein clusterin, thereby **sensitizing prostate cancer cells to chemotherapy**. Custirsen is now in Phase III trials of combination therapies.



Clinical Research

- G-202 – a Thapsigargin-based Prostate Specific Membrane Antigen (PSMA)-activated prodrug, developed by Dr. Samuel Denmeade and colleagues, couples a PSMA-specific peptide to the analog of the plant-derived toxin Thapsigargin. The prodrug is inactive/non-toxic until it encounters the enzyme, PSMA, expressed on the surface of prostate cancer cells, at which point it is activated and **selectively kills tumor cells with minimal side effects**. A Phase II clinical trial of G-202 in patients with metastatic CRPC has been approved.
- APC-100 – a small molecule inhibitor of the AR derived from vitamin E by Dr. George Wilding **inhibits the growth of both androgen-dependent and -independent prostate cancer**, delays tumor progression and increases survival in pre-clinical studies. APC-100 is now in a Phase I/II clinical trial at the University of Wisconsin and Wayne State.
- Ipilimumab – preclinical and clinical studies by Dr. Eugene Kwon and the PCCTC demonstrated that anti-cytotoxic lymphocyte antigen-4 (CTLA-4) antibody, a potent inhibitor of T cell mediated immunity **enhances treatment response to androgen deprivation therapy**, is now in Phase III clinical trials.
- Cabozantinib (XL184) – a small molecule inhibitor of multiple receptor tyrosine kinases is now in Phase III clinical trials after Phase II trials performed by the PCCTC in patients with metastatic CRPC showed promise in **decreasing bone metastases and associated pain**.
- 3,3'-diindolylmethane (DIM) – a natural derivative of indole-3-carbinol (I3C), which is found in cruciferous vegetables (e.g., broccoli, cabbage). Research by Dr. Stephen Safe suggests that DIM and ring-substituted DIM isoforms differentially modulate androgenic response in prostate cancer, and that it can be customized for anti-androgenic activity. Data from Dr. Fazlul Sarkar's lab suggests that DIM inhibits nuclear localization of NF-κB activity. DIM is now in several Phase I and Phase I/II clinical trials for prostate cancer. Dr. KM Rahman showed that **DIM in combination with Taxotere inhibited tumor growth by 80% in an animal model**.
- EP-100 – a membrane disrupting peptide **targeted to prostate (and other) cancers** overexpressing LH/RH receptor developed by Dr. Carola Leuschner completed a Phase I clinical trial in solid tumors, and a Phase II trial has been initiated in ovarian cancer with subsequent trials likely in prostate and other cancers.

Improvements for Patients

- Abiraterone acetate (ZYTIGA™) – an FDA-approved anti-androgen for the **treatment of metastatic CRPC**. The PCRP supported the clinical testing of ZYTIGA through the PCCTC.
- MDV3100 (Xtandi™) – an FDA-approved AR inhibitor that blocks testosterone activity on the AR in **metastatic CRPC** patients who were previously treated with chemotherapy (docetaxel).
- MR Imaging Based Treatment Planning for Radiotherapy of Prostate Cancer – Developed by Lili Chen at the Fox Chase Cancer Center, this treatment protocol **decreases the duration, radiation exposure and costs for radiotherapy treatment**.
- Denosumab (XGEVA™) – an FDA-approved antibody that **slows the progression of prostate cancer bone metastases**. Early preclinical studies by Dr. Evan Keller and supported by the PCRP showed that antibodies blocking the bone resorption protein RANKL was effective in slowing bone loss during cancer treatment.
- VELCADE® – The **PCRP supported preclinical studies** on PS-341, a proteasome inhibitor. Results of this study were used to design a Phase I clinical trial. Millenium Pharmaceuticals Inc. now manufactures this drug as VELCADE®. Despite failing as a drug candidate for prostate cancer, VELCADE® is approved for the treatment of multiple myeloma and relapsed mantle cell lymphoma.
- Elekta Synergy® – Dr. David Jaffray and colleagues developed and patented a high-precision cone-beam computed tomography (CT) imaging system capable of pinpointing the current position of the prostate and support structures to **deliver high doses of radiation to a tumor while minimizing damage to adjacent normal tissues**. This invention was licensed to Elekta, LTD (United Kingdom) which manufactures Elekta Synergy, received FDA clearance in 2003, and has since been used to treat prostate and other cancers in the U.S., Canada and Europe.

BIOLOGY OF DISEASE RESISTANCE AND DEVELOPING NEW MODELS FOR TREATMENT

Patients with advanced prostate cancer fear progressing to castration-resistant prostate cancer because they face a lack of treatment options. Therefore, a critical question to answer is: What triggers the transition to the castrate-resistant disease? Understanding the biological mechanisms involved is the focus of many PCRP-funded investigators. These basic scientists and clinicians are working to understand the cellular and molecular mechanisms of resistance and disease progression while simultaneously developing the next generation of clinical compounds that may prolong survival and overcome resistance in patients with advanced disease. Featured below is just some of the pivotal work PCRP investigators are conducting on disease resistance and potential new forms of therapy.



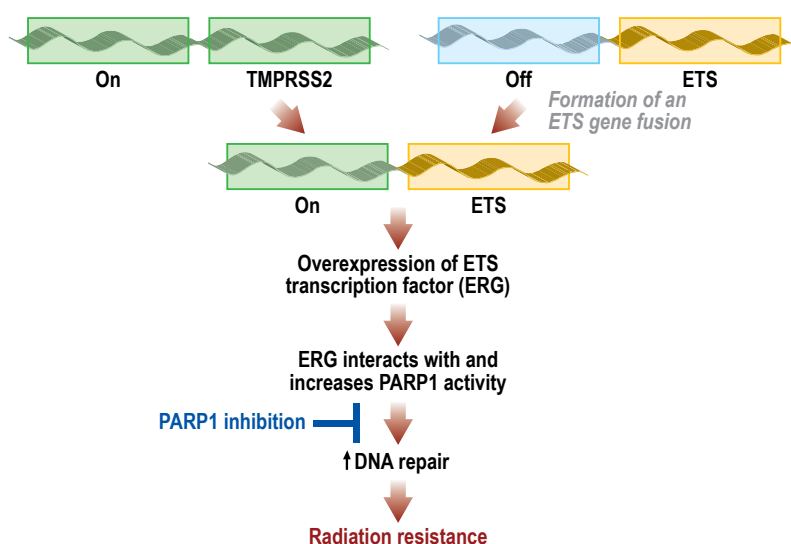
ETS Gene Fusions as Predictive Biomarkers of Resistance to Radiation Therapy for Prostate Cancer

Felix Feng, M.D., University of Michigan

Radiation therapy is a common treatment approach for men diagnosed with prostate cancer, and allows many men to live without disease recurrence. However, some prostate cancers show resistance to radiation therapy, and identifying this before treatment could facilitate better treatment decision making. Dr. Felix Feng at the University of Michigan, recipient of an FY09 Physician Research Training Award, demonstrated in laboratory models of prostate cancer that the ETS gene fusion, present in more than half of all

human prostate cancers, can cause resistance to radiation therapy. In collaboration with his mentor, Dr. Arul Chinnaiyan, Dr. Feng's early studies revealed that the ETS gene fusion product, known as ERG, physically interacts with key DNA repair proteins such as DNAPK. Because DNA repair is central to the response of prostate cancer to radiation therapy, Dr. Feng used survival assays to compare the response of ERG-positive versus ERG-negative prostate cancers to radiation. Blocking these DNA repair pathways reversed the radiation resistance. These initial experiments revealed that ERG causes radiation resistance by affecting the repair of DNA damage, and that this resistance can be overcome by blocking DNAPK in the DNA repair pathway.

With support from his PCRP award, Dr. Feng continues to pursue a new approach to treat prostate cancers driven by the ETS gene fusion by targeting DNA repair pathways to reverse radiation resistance. This investigation suggests that ETS gene fusions may serve as predictive biomarkers of resistance to radiation therapy in prostate cancer. They also provide a means to identify development of radioresistance in the tumor or determine if treatment should be intensified. As this research project continues, Dr. Feng is also developing plans to initiate clinical trials that will assess how well these approaches can work in patients.

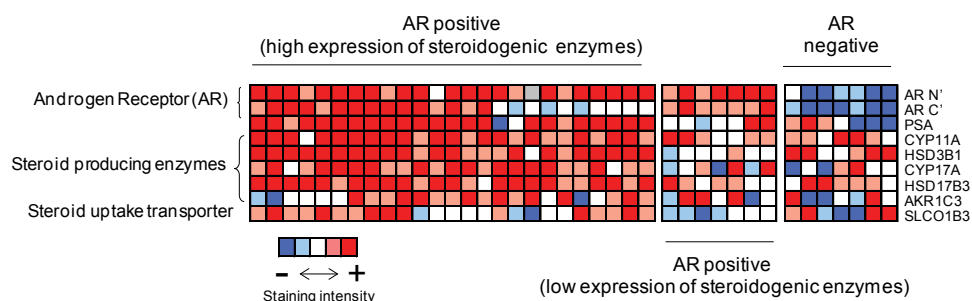




Optimizing Treatment of Advanced Prostate Cancer and Exploiting Mechanisms Driving Castration Resistance

Elahe Mostaghel, M.D., Ph.D., Fred Hutchinson Cancer Research Center

Testosterone suppression, which results from androgen deprivation or anti-androgen therapies, remains the most effective therapy for advanced prostate cancer, but often results in the development of castration-resistant disease. Dr. Elahe Mostaghel at the Fred Hutchinson Cancer Research Center observed that despite treatments which effectively suppress blood testosterone levels, levels within tumor metastases from men who had died of advanced prostate cancer were quite high. Levels of AR and of steroid synthesizing enzymes and transport proteins were also elevated, suggesting intratumoral androgen as a factor in resistance to anti-androgen therapies. Dr. Mostaghel received an FY09 New Investigator Award to study the biology of the prostate cancer cell as it develops resistance, and one important aspect of her project addresses the paradoxical observation that the growth of some recurrent prostate tumors is actually inhibited rather than stimulated by very high doses of testosterone. Because testosterone suppression causes many side effects, the ability to treat prostate cancer with high-dose testosterone therapy could significantly alleviate these side effects. Using a mouse xenograft model of human prostate cancer, Dr. Mostaghel is dissecting tumor characteristics associated with response to this treatment strategy to identify patients that would respond positively to high-dose testosterone treatments. Dr. Mostaghel is also the recipient of FY10 and FY11 Idea Development Awards, and an FY11 Exploration-Hypothesis Development Award to fund recently initiated investigations of unique issues in castration resistance. In total, these studies will provide important insight into optimizing both current and future prostate cancer therapies.



Expression of the androgen receptor (AR), steroid producing enzymes and a steroid uptake transporter in the metastases from men with castration-resistant prostate cancer. Each column represents the average staining intensity for the indicated protein in the metastases of one patient. Groups of tumors can be identified which could potentially guide treatment decisions: 1) AR positive tumors with high expression of steroid producing enzymes. These tumors would be expected to respond to abiraterone (Zytiga), which inhibits steroid synthesis. 2) AR positive tumors with low expression of steroid producing enzymes. These tumors would be expected to respond to MDV3100 (Enzalutamide), which blocks activity of the AR itself; and 3) AR negative tumors. These would not be expected to respond to drugs targeting steroid production or the AR, but would require other treatments such as chemotherapy.



"The PCRP, with the guidance from the experts serving on its Integration Panel, has set its sight and focus on the overarching challenge 'Develop effective treatments and address mechanisms of resistance for men with high-risk or metastatic prostate cancer.' As recently as 10 years ago, men suffering from castration-resistant metastatic prostate cancer had few treatment options, and those were mostly palliative in nature. In the past several years, through the dedicated work of clinicians and scientists focusing on prostate cancer, and the support of organizations such as the DoD, novel treatments are now available that have not only improved the quality of life but the outcomes as well for men afflicted with this disease. One reason for this, and for the optimism that newer and more effective treatments will be developed, is the focus on this overarching challenge and the different, innovative approaches that researchers are taking to address this. Through continued congressional support of the PCRP and its two-tier review process, funding remains available to achieve these goals by providing the necessary resources to the best and brightest researchers who are dedicating their careers to improving the lives of men with prostate cancer."

Philip Arlen, M.D., Chief Executive Officer, Neogenix Oncology, Inc.



The Function of AR-Negative Cancer Stem Cells in Prostate Cancer

Susan Kasper, Ph.D., University of Cincinnati

All too often, prostate cancer returns after having been “cured” by surgery and AR therapy (ADT). Increasing evidence is pointing to a small tumor cell population called ‘prostate cancer stem cells’ (or CSCs) as the basis for cancer recurrence. Prostate CSCs are able to resist the drugs that kill rapidly dividing cells which make up the bulk of a tumor, and a potential cause for this may relate to the fact that prostate CSCs do not express the AR and are thus resistant to ADT, allowing the tumor to regrow.

Dr. Susan Kasper was interested in studying why prostate CSCs do not express AR. Through her FY07 Idea Development Award, she found that CSCs actively degrade AR protein through proteasomal degradation. By treating cells with proteasome inhibitors to prevent this degradation, she observed that CSCs rapidly lost their stem cell characteristics, and cell death occurred within 72 hours of treatment. These observations suggest that ADT-resistant CSCs could potentially be eliminated from prostate tumors by proteasome inhibitors.

Dr. Kasper is now using an animal model to develop a combination therapy approach.

Animals with human CSC xenograft tumors will be treated with ADT and a proteasome inhibitor to determine whether combinatorial therapy will eliminate ADT-resistant tumors. As a potential treatment strategy, the concept of inducing AR may appear counterintuitive to ADT. However, since a tumor is composed of many cell types, the most successful treatment strategies are likely to include approaches that treat all cell populations within the tumor, including CSCs.

“PCRP funding has allowed us to study this more unconventional approach of inducing AR protein expression with the aim of eliminating CSCs and causing permanent tumor regression.”

Susan Kasper, Ph.D.

MMPs Impact Bone Responses to Metastatic Prostate Cancer

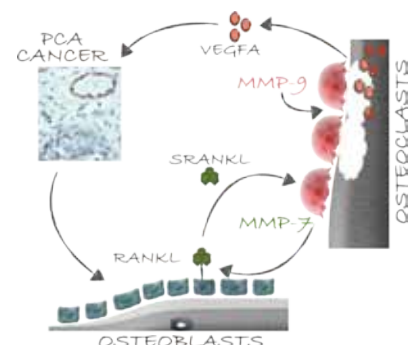
Conor C. Lynch, Ph.D., Moffitt Cancer Center

In bone, prostate cancer metastases generate painful lesions comprised of areas of rapid bone destruction and formation that are currently incurable and greatly affect the patient’s quality of life. By studying how prostate metastases manipulate the normal cells of the

“The New Investigator Award (NIA) offered by the PCRP has been essential in allowing me to become an independent and established prostate cancer research investigator. The results generated from the award were critical in facilitating my successful application for NCI RO1 funding. Since completing my NIA project, I have taken a new position at the Moffitt Cancer Center in Tampa, where my laboratory is continuing this important line of research – identifying cures for prostate to bone metastases.”

Conor Lynch, Ph.D.

bone to induce these lesions, Dr. Conor Lynch hopes to make discoveries that will lead to the generation of new therapies to prevent bone metastases. Based on his early data identifying significant increases in the expression of enzymes known as matrix metalloproteinases (MMPs), Dr. Lynch earned an FY06 New Investigator Award to investigate in animal models whether these MMPs contributed to disease progression. Findings from this study identified that individual MMPs play very specific roles in the context of the prostate cancer-bone microenvironment, including changes in pathways for destruction of bone cells and vascularization of the tumor-bone microenvironment. As a result of his PCRP award, Dr. Lynch was able to secure additional funding from the NIH which allowed him to continue work on this project. In conjunction with additional collaborators, Dr. Lynch’s laboratory is currently working to test the efficacy of selective MMP inhibitors in animal models of prostate cancer metastases to bone. In addition, in collaboration with Dr. David Basanta, computational biology approaches are being used to predict the effect of potential therapeutics on prostate cancer-induced bone lesions.



EMERGING IMAGING TECHNOLOGIES IN PROSTATE CANCER MANAGEMENT

Advances in technologies for the detection, treatment, and prognosis of prostate cancer have deepened our understanding and enhanced targeting of therapeutics in the management of prostate cancer. Improvements in energy delivery systems and new imaging techniques, including molecular imaging, are leading to the design and production of tools that will allow clinicians to better localize and detect disease, and derive a more accurate patient prognosis following treatment. Improved imaging will be less invasive, monitor molecular events simultaneously, increase precision in delivering therapy, and enhance pathological assessment of disease progression so that follow-up treatments can be better tailored to each patient.

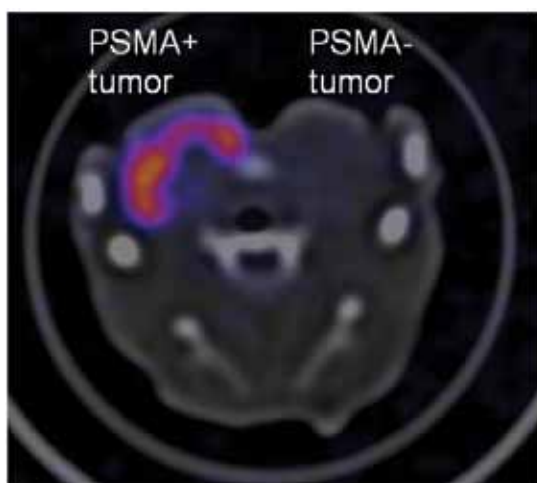


Development of Novel Self-Wrapping PSMA Ligands for Use in Imaging and Therapy of Prostate Cancer

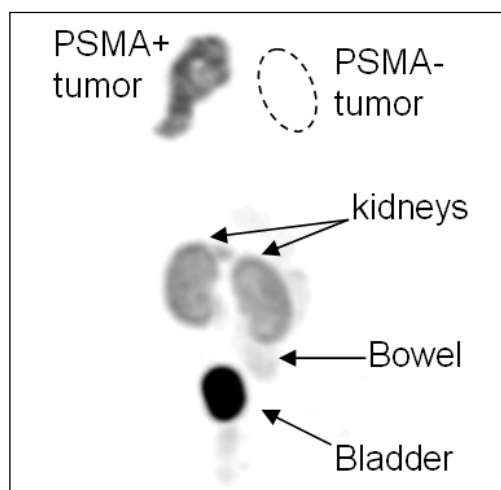
Steve Huang, M.D., Cleveland Clinic Foundation

Although prostate biopsy is necessary to diagnose prostate cancer, it can be accompanied by discomfort, bleeding, and localized infection, as well as the risk of false negative results. At the Cleveland Clinic, FY09 New Investigator Award recipient Dr. Steve Huang has focused his research on developing a non-invasive, sensitive, and specific method of localizing cancer in its early stages to reduce the need for invasive biopsies. In his laboratory, efforts were made to engineer tighter binding derivatives of small molecules

that target PSMA, a protein that is expressed on the membrane of prostate cancer cells. Based on these studies, Dr. Huang designed a molecular framework that can specifically target prostate cancer cells by selectively binding PSMA. The PSMA binding molecules, or ligands, are easy to prepare, and can be used to localize cancer cells in the prostate using conventional imaging techniques. Dr. Huang recently constructed a technetium-99m (Tc99m) radiolabeled PSMA ligand and demonstrated tumor-specific targeting in vivo in imaging and biodistribution studies using a mouse xenograft model of prostate cancer. As therapeutic agents can also be linked to these PSMA ligands for targeted delivery of the therapeutics directly to the cancer cells, he plans to study the ability of the PSMA targeted tracer to become internalized, which would serve as an initial indication of its therapeutic potential. The results of this research will help to move the new PSMA ligands towards future pre-clinical studies for safety determination, with the ultimate goal of use in patients and reducing or eliminating the need for conventional biopsy.



An axial slice of the fused micro SPECT/CT images showing uptake in PSMA+ tumor, but not the PSMA- tumor.



The whole body maximal intensity projection image from microSPECT of a tumor-bearing mouse four hours after injection of our tracer.



Feasibility of Dual Optics/Ultrasound Imaging and Contrast Media for the Detection and Characterization of Prostate Cancer

David Hall, Ph.D., University of California, San Diego

When prostate cancer is first diagnosed, it is important to have accurate grading of the tumor so that optimal treatment decisions can be made. Currently, the best method for evaluating tumor grade is by obtaining multiple biopsy samples, which can be a painful procedure. However, these samples may not provide a wholly accurate representation of the prostate tumor. Thus, new technologies are being investigated with the intent to guide and improve the accuracy of biopsy procedures. Ultrasound is a widely used technology

for visualizing tumors for biopsy procedures, but scientists are hoping to expand this technology from basic guidance for biopsies towards use for advanced screening and tumor characterization. Dr. David Hall used the support of his FY06 Idea Development Award to combine ultrasound and optical methods, acousto-optic, with the ultimate goal of improving optical imaging of tumor oxygen levels for the detection and characterization of prostate cancer. Dr. Hall and his collaborators at the University of California, San Diego developed new acousto-optic systems which were enhanced with fluorescent microbubbles and tested them with in vitro experiments. The results demonstrated significantly enhanced acousto-optic signals which are highly promising for the ultimate goal of this innovative methodology. Dr. Hall and his collaborators plan to optimize this approach and move towards in vivo experiments.





Team Photo (from left to right): Shyam Natarajan, Ph.D., postdoctoral researcher, Department of Surgery; Warren Grundfest, M.D. F.A.C.S., principal investigator and Professor of Bioengineering, Electrical Engineering, and Surgery; Martin Culjat, Ph.D., co-investigator and Adjunct Assistant Professor of Bioengineering and Surgery; Rahul Singh, Ph.D., co-investigator and Adjunct Assistant Professor of Bioengineering and Surgery.

Ultrasound Imaging System for Prostate Cancer

Warren Grundfest, M.D., University of California, Los Angeles

Transurethral ultrasound (TUUS) is a new method of imaging the prostate in real-time 3D. By imaging the prostate from within, TUUS can achieve higher resolution, improved visualization of the anterior prostate, and motion-independent imaging, thus providing advantages over the use of conventional transrectal ultrasound (TRUS) imaging. Dr. Warren Grundfest, an FY09 Idea Development Award recipient, and his research team at the University of California, Los Angeles (UCLA) have undertaken simultaneous engineering and clinical efforts to accelerate development of a TUUS imaging device. Through a unique collaboration involving the Departments of Biomedical Engineering, Urology, Radiology, Surgery, and UCLA's Center for Advanced Surgical and Interventional Technology, Dr. Grundfest's research efforts have resulted in the fabrication of a catheter-based 3D imaging device.

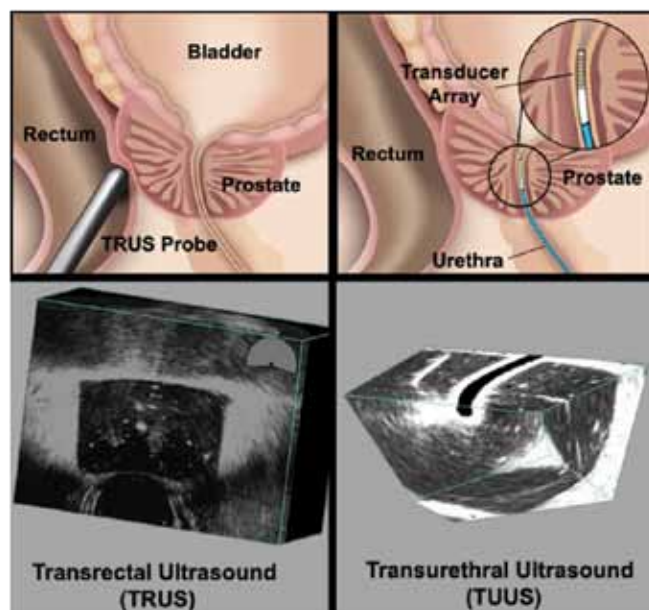
His research team has designed an ultrasound imaging system capable of utilizing novel signal processing techniques not currently possible with existing ultrasound systems. Image reconstruction methods were also developed and validated in simulations and phantoms to enable real-time 3D imaging of the prostate using TUUS. Further studies showed that this modality could be combined with traditional MRI methods to provide improved real-time information to the clinician for localizing and treating prostate cancer without the use of cumbersome tracking systems. Fusing the 3D images with CT or MRI will enable enhanced targeting and treatment of prostate cancer focally, and could reduce the need for open prostate surgery. As the project moves forward, Dr. Grundfest and his collaborators are currently fabricating ultrasound transducer arrays for the imaging catheters using microelectronics technology in order to optimize and miniaturize these prostate imaging devices for future clinical trials.



"I was so happy to review grants for the DoD PCRP. My very first grant was a PCRP New Investigator Award - it gave me a fabulous start to my career and set the scene for my research program. It was wonderful to give

back by reviewing and hopefully setting today's new investigators down a productive and exciting career path."

Jason Lewis, Ph.D., Memorial Sloan-Kettering Cancer Center



Comparison of conventional prostate imaging using TRUS (upper left) with 3D TUUS (upper right), a novel imaging method developed at UCLA. Imaging studies were conducted in prostate phantoms using TRUS (lower left) and TUUS (lower right).

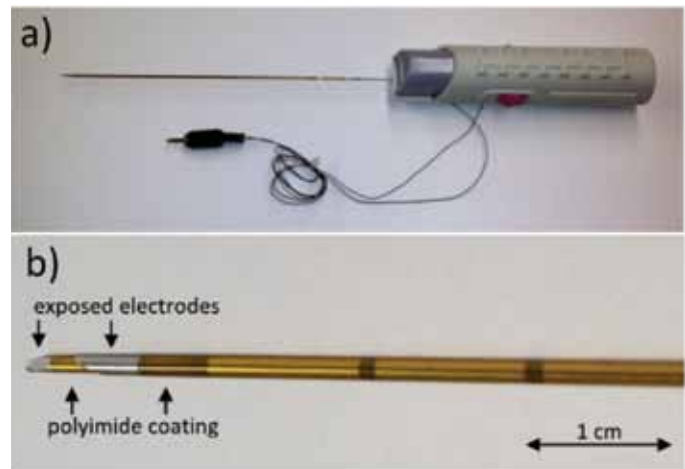


Incorporating Electrical Property Sensing Into a Clinical Biopsy Needle for Enhanced Prostate Cancer Detection

Ryan Halter, Ph.D., Dartmouth College

The technology of electrical impedance spectroscopy (EIS) has proven to be a successful method for differentiating cancer from normal prostate tissues. EIS detects the changes in cellular structure that occur as normal prostate cells become cancerous and as the tumor continues to grow. Dr. Ryan Halter first received funding from the PCRP to study the electrical properties of prostate cancer through an FY06 PCRP Prostate Cancer Training Award while he was a postdoctoral fellow at Dartmouth College. With support from his

training award, he was able to demonstrate significant electrical property differences between different Gleason grades of prostate cancer. Dr. Halter then successfully competed for an FY08 PCRP New Investigator Award, which allowed him to take a significant step in translating this laboratory finding to a clinical device. Specifically, he developed a novel sensor that integrates with standard needles for prostate cancer biopsy so that it can measure electrical properties at the needle tip at the same time as tissue cores are extracted. Such adaptation of biopsy needles with this technology would enable doctors to better identify potentially cancerous regions of the prostate for biopsy, thus providing a broader assessment of the gland as compared to typical biopsy protocols. To date, Dr. Halter and his colleagues have constructed over 50 of these devices, and recorded data from approximately 35 ex vivo prostates, verifying that they are able to distinguish between cancer and benign regions of the prostate. Dr. Halter is currently working to obtain additional funding for further development of this device, and has the goal of delivering an approved product for clinic use in as little as five years.



EIS-Bx probe design, with polyimide insulation used in clinical phase of the program.



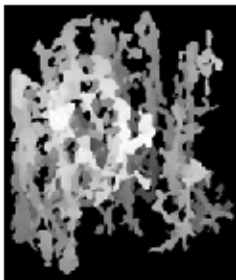


Virtual Bone Biopsy: A Novel Technique to Assess Skeletal Integrity in Men with Prostate Cancer

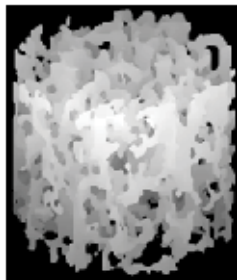
Susan Greenspan, M.D., University of Pittsburgh

One in 5 men will have an osteoporotic fracture after age 50, and this is increased in men with prostate cancer on androgen deprivation therapy, a common treatment for prostate cancer. Bone fractures are a critical issue in these patients, since men who experience fractures have lower survival rates than men who do not. While the best test for predicting osteoporosis is by assessing bone mineral density by dual energy X-ray absorptiometry

(DXA), it has been observed that many men who experience vertebral (spine) fractures are the ones not diagnosed with osteoporosis by DXA. This is presumably due to the fact that the majority of vertebral fractures are silent, and DXA is not able to measure all factors that contribute to bone strength and fractures, such as bone microarchitecture. The current standard method to assess bone microarchitecture is with a painful and invasive bone biopsy procedure. Dr. Susan Greenspan sought to re-evaluate the current paradigm for assessing fracture risk in men by using a new virtual bone biopsy technology. With support from an FY06 PCRP Idea Development Award, Dr. Greenspan's team at the University of Pittsburgh recruited prostate cancer patients on androgen deprivation therapy who had suffered a



Fracture



No Fracture

vertebral compression fracture, and compared them to men who had not. A virtual bone biopsy test was performed using a high-resolution MRI with a coil around the patient's wrist, and DXA measurements and conventional spine X-rays were also collected. The study results showed that this novel technique of virtual bone biopsy provided additional information beyond the standard DXA on the risk for fracture in men with prostate cancer on androgen deprivation therapy. Dr. Greenspan hopes to use more advanced MRI machines to provide even better visualization of the bone microstructure, and also plans to test this procedure in a weight-

bearing bone such as the leg, where the microarchitecture will likely have an even greater contribution to bone strength. Developing better approaches to predict the risk of bone fracture will enable physicians to tailor preventive approaches to the patient and spare men undergoing prostate cancer therapy from the debilitating impact of this side effect.



Opportunities for Improved Decision-Prostate Cancer Health Disparities:

African American (AA) men are twice as likely as men in other ethnic groups to die from prostate cancer. It is absolutely critical to develop a better understanding of this disparity so that it can be eliminated. Although some contributing factors are known to include race, age, biology, socioeconomic status, or cultural influences, PCRFP-funded scientists are conducting important assessments of these and other factors to identify the critical contributors while also identifying barriers to treatment and strategies to address prostate cancer's disproportionate effects on AA men.

The North Carolina-Louisiana Prostate Cancer Project (PCaP)



In 2002, the PCRFP funded Dr. James Mohler to establish a landmark consortium that would investigate racial differences in prostate cancer. Researchers from six institutions collaborated to uncover the reasons why prostate cancer mortality is higher in AAs than in Caucasian Americans (CA). The study focused on (1) interactions with the health care system, (2) diet and biology of the patient, and (3) characteristics of the tumor, and it yielded invaluable information that is helping to focus public health efforts on reducing racial disparities in prostate cancer, thereby improving survival. Thirteen years later, the biorepository of patient samples and the corresponding database of clinical, epidemiological, and interview data from participants of the study, which have been made available to the research community (<http://ncla-pcap.org/>), are still being utilized to fuel studies regarding the genetic, environmental, and social causes of prostate cancer risk, especially those responsible for the disproportionate incidence and death rate among AA men.

Recent PCaP Discoveries:

- ***AA men tend to be younger than CA men at age of diagnosis and are more likely to have a more aggressive cancer.***
- ***CA men place greater trust in their physicians, more often see the same physician, and are more likely to have had past prostate cancer screenings than AA men. These results suggest that efforts to improve preventative care and continuity of care are an important route to reducing racial disparities.***
- ***In both AA and CA men, obesity is associated with more aggressive prostate cancer. However, AA men have more aggressive prostate cancer in general than CA men even at normal weight.***
- ***Mental distress after prostate cancer diagnosis is higher in men with lower health literacy levels, indicating that interventions targeting this group of patients may improve their health-related quality of life.***

Making to Reduce

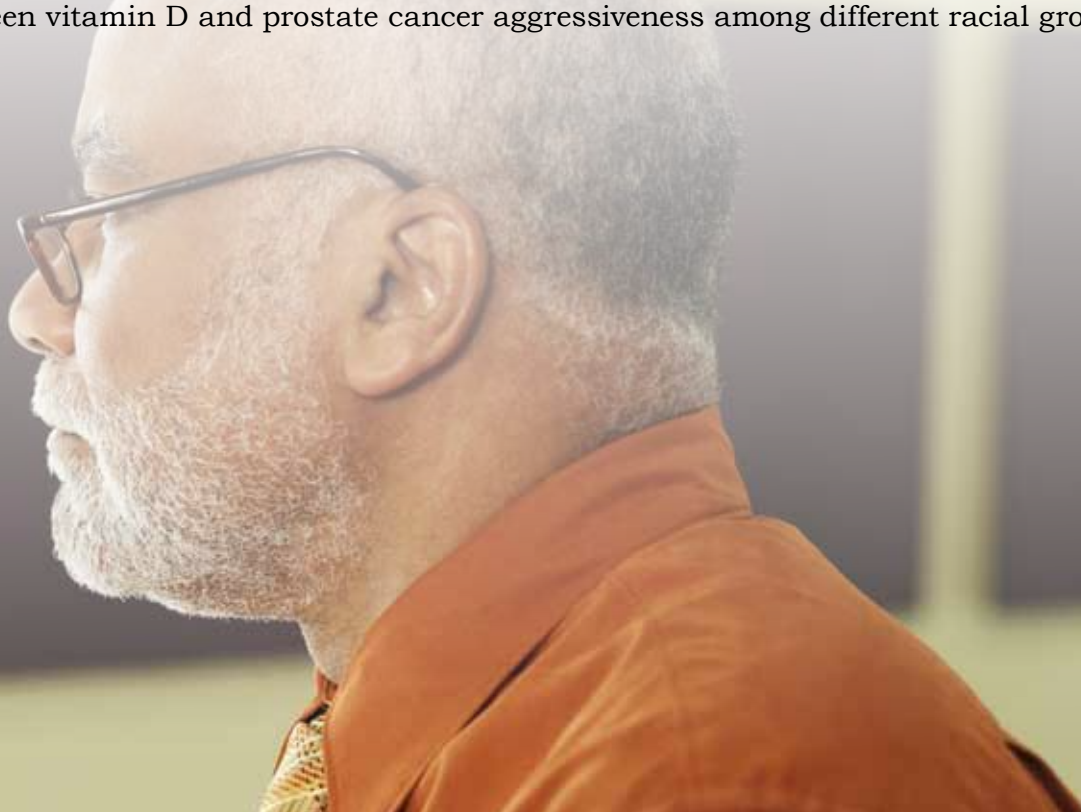
- ***With respect to treatment decision-making, clinicians need to tailor their interventions according to the patient's age and cancer aggressiveness, discuss the physical impact of treatment to reduce concerns and misconceptions, and provide adequate time and assistance to patients when considering treatment options and information from different sources.***

Ongoing PCaP Studies:

The PCRP has funded two PCaP ancillary studies investigating the relationship between race, genetics, and prostate cancer aggressiveness.

Identification of genetic causes for prostate cancer susceptibility has been a challenge for the research community, perhaps attributable to the fact that some susceptibility genes may be located in mitochondrial DNA rather than in nuclear DNA. Even more intriguingly, AA men are at a disproportionately higher risk for many oxidative stress-related medical conditions, including prostate cancer, indicating that the racial disparity of prostate cancer could be due, in part, to genetic variation of mitochondrial DNA. Drs. Hua Zhao and Jeannette Bensen are investigating the role of genetic variation in the mitochondria as a factor related to prostate cancer aggressiveness; their findings may have a significant impact on cancer research.

The relationship between vitamin D and prostate cancer is currently an intensely studied subject. The major source of vitamin D in humans results from exposure to ultraviolet (UV)-B rays from sunlight; individuals with darker skin pigmentation require longer time in the sun to produce an equivalent amount of vitamin D as that produced by individuals with lighter skin pigmentation. Dr. Susan Steck is using PCaP data and specimens to examine the association between vitamin D and prostate cancer aggressiveness among different racial groups.



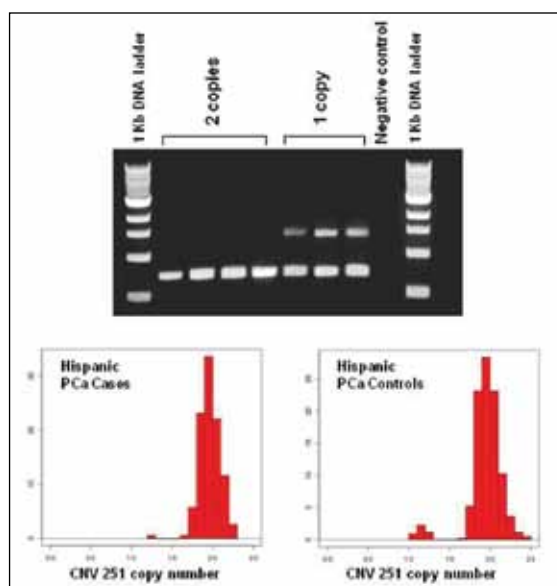


Assessing the Role of Copy Number Variants in Prostate Cancer Risk and Progression Using a Novel Genome-Wide Screening Method

Donna Lehman, Ph.D., University of Texas Health Science Center, San Antonio

The increased incidence of prostate cancer within families suggests that genetic factors influence the risk for development and progression. Genetic differences also vary by ethnicity, although this area of research has historically been understudied, especially in the case of Mexican Americans, for whom little is known regarding the genetic risk factors for prostate cancer. One type of genetic factor that can contribute to prostate cancer

development is copy number variation (CNV). CNVs can affect the expression of genes or alter the local genomic architecture, thereby potentially playing a substantial role in cell behavior through numerous downstream changes. Dr. Donna Lehman of the University of Texas Health Science Center at San Antonio received an FY08 Idea Development Award to perform the first genome-wide association of CNVs and risk for prostate cancer in Mexican American subjects from the San Antonio Biomarkers of Risk for Prostate Cancer (SABOR) study. She and her colleagues genotyped ~750,000 markers across the genome in prostate cancer cases and control subjects, and identified 462 CNVs that were polymorphic in at least two individuals. One CNV of particular interest was a rare, non-recurrent 8,486 base-pair deletion on the chromosome 8q24, which was associated with decreased prostate cancer risk in 989 Mexican American men. Only 3 of 1530 Caucasian men carried the deletion, indicating that this deletion is not likely to affect risk in the Caucasian population. The deleted sequence contains a putative conserved transcription factor binding site for NKX3.1, an androgen-regulated gene involved in prostate cancer development and stem cell maintenance. Dr. Lehman's group is continuing to investigate the significance of this deletion and its implication for prostate cancer risk assessment. She hopes to continue this research in other populations to help address why risk for prostate cancer varies between populations. Her investigations on the mechanisms of how associated genetic variants modify risk for prostate cancer could lead to improved treatment decision-making and potentially new treatment strategies as well.



Genotyping of CNV 251 deletion in San Antonio Cohorts. Gel electrophoresis of PCR products, generated with nested primers, displaying genotype states of the deletion. Negative control indicates no DNA. Histogram of calculated copy number values from qPCR assays. Gaussian distributions are present representing integer copy number values 0, 1 and 2.

"Serving as a peer reviewer for the DoD has been an enjoyable learning experience for me. My colleagues from various institutions bring a wealth of knowledge and empathy to the review process. The contributions of consumers with equal voice and equal vote keeps the focus on the thing that matters most – making a real difference in the lives of cancer survivors and their loved ones."

**Charnita Zeigler-Johnson, Ph.D.,
University of Pennsylvania**

Pictured on page 25



Multilevel Analysis of Neighborhood Characteristics and Prostate Cancer Severity

Charnita Zeigler-Johnson, Ph.D., University of Pennsylvania

AAs have the highest incidence of prostate cancer and present with aggressive disease at higher rates than other racial and ethnic populations. Many factors have been hypothesized to contribute to this health disparity, yet there are few if any factors that definitively provide an opportunity to begin reducing prostate cancer disparities. However, one area of research has been focused on the contribution of socio-economic status (SES), since, compared to European Americans (EAs), AA men are more likely to reside in neighborhoods with a lower SES. With funding from an FY08 Health Disparity Research Early Career Investigator Award, Dr. Charnita Zeigler-Johnson examined the relationship between neighborhood characteristics and prostate cancer severity by using U.S. Census Bureau information on anonymized prostate cancer survivors' residential locations, including local crime databases and ecological variables. Study results showed a strong association between men diagnosed with more advanced prostate cancer and greater neighborhood deprivation, particularly among AA men. Using patients from the Study of Clinical Outcomes, Risk and Ethnicity, Dr. Zeigler-Johnson utilized methodologies developed with the University of Pennsylvania Cartographic Modeling Laboratory to further investigate the relationship between neighborhood and patient-level factors, such as age, race, and type of treatment received, on prostate cancer severity. Dr. Zeigler-Johnson plans to use the information from this study to create cluster maps that would target specific communities for tailored interventions. These maps will also allow investigators to visualize other environmental factors that may not be obvious from analytic models alone. Dr. Zeigler-Johnson credits the PCRP for providing funding which allowed her to gain experience in this area of research and to develop preliminary data to develop her hypothesis, the results of which have also helped her to obtain additional funding from the Resource Centers for Minority Aging Research to continue this work.



Nuclear Matrix Proteins in Disparity of Prostate Cancer

Asim Abdel-Mageed, D.V.M., Ph.D., Tulane University

Differences in socioeconomic factors, diet, education, and access to care have been cited as some of the key factors contributing to prostate cancer health disparity; yet a greater understanding of these and other factors is still needed to begin to solve the problem that AA men are more than twice as likely to die from prostate cancer than EA men. Even in populations of AA and EA men with similar SES, there is still a much greater risk of prostate cancer incidence and mortality in AA men, suggesting other biological or genetic factors are involved. Dr. Asim Abdel-Mageed, recipient of an FY08 Health Disparity Research Award, set out to understand the differences in protein levels between AA and EA men diagnosed with prostate cancer, and discovered that the presence of certain proteins is correlated to differences in disease progression between AA and EA men. One protein that particularly stood out from this group was heterogeneous nuclear ribonucleoprotein H1 (hnRNPH1), and therefore Dr. Abdel-Mageed conducted functional studies of hnRNPH1 to demonstrate that it physically interacts with and induces activation of the AR, a molecule that plays a key role in prostate cancer development and is a major target for hormone-based therapeutics. This interaction was also observed to be independent of the presence of androgen, possibly linking hnRNPH1 to the more aggressive hormone-independent prostate cancers. Dr. Abdel-Mageed's work provides evidence that the AR-hnRNPH1 axis represents a previously uncharacterized mechanism that may contribute to therapeutic resistance and ethnic disparity in prostate cancer. In addition to its potential clinical utility as a biomarker or prognostic indicator of aggressive disease, therapeutic targeting of hnRNPH1 may offer a new approach to overcoming resistance to hormone therapy in this group of patients.

UNDERSTANDING THE GENETICS OF PROSTATE CANCER AND IDENTIFICATION OF BIOMARKERS FOR DISEASE PREDICTION AND TREATMENT

Whole genome sequencing data from human cancers are revealing the mutations and gene families present in those who are at high risk of developing prostate cancer. New technologies and techniques in genomics and proteomics have resulted in the discovery of various biomarkers that are currently being tested with the goal of developing new aids for diagnosis, prognosis, and treatment decisions for prostate cancer patients.



Targeting the Kinase-Independent, Prosurvival Function of EGFR in Prostate Cancer

Zhang Weihua, Ph.D., University of Houston

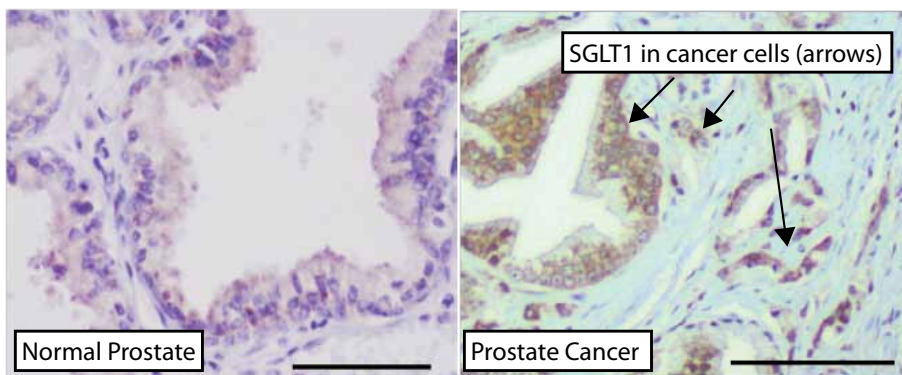
In comparison to normal cells, prostate cancer cells consume higher amounts of energetic substrates and nutrients such as glucose. This high level of energy consumption is thought to not only contribute to the survival of the cancer cell but to also be responsible for the development of cachexia, a devastating cancer symptom characterized by significant loss of appetite, uncontrollable weight loss, muscle atrophy, fatigue, and weakness, which in many cases results in death. A key discovery by Dr. Zhang Weihua and his colleagues at the University of Houston was that the epidermal growth factor

receptor (EGFR) helps cancer cells to uptake high levels of glucose. While EGFR has been explored as a therapeutic target for prostate cancer, these therapies have focused on a separate function of EGFR – its tyrosine kinase activity – and have not resulted in much improvement over current therapies. Thus, Dr. Weihua's discovery of this new role of EGFR in cancer cell survival through glucose uptake provided a new therapeutic approach for both cancer treatment and symptom management of cachexia.

With support from an FY09 New Investigator Award, Dr. Weihua led his laboratory in conducting a series of investigations to test the effects of disrupting the glucose uptake of EGFR. One molecule of interest was SGLT1, a protein that assists EGFR with the transport of glucose.

Dr. Weihua observed that SGLT1 is also over-expressed in prostate cancer and could therefore have potential as a therapeutic target.

Dr. Weihua's team has now mapped the SGLT1 interaction domain in EGFR in order to design interfering peptide molecules that will disrupt the interaction of EGFR and SGLT1, a strategy that is already gaining interest from the pharmaceutical industry, and they hope to test the effectiveness of these inhibitors in animal models in the near future.

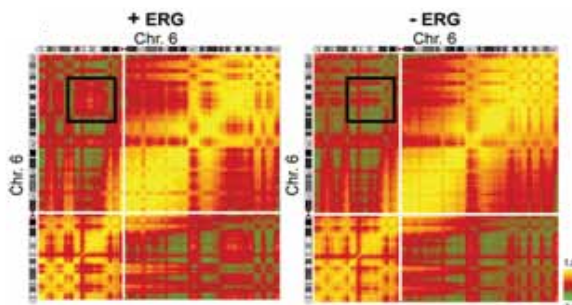




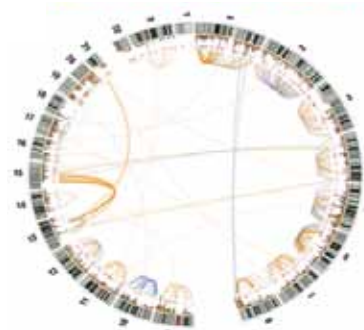
Using Chromosome Structure to Better Understand the Role of TMPRSS2-ERG Variants in Prostate Cancer Progression

David Rickman, Ph.D., Cornell University, Weill Medical College

DNA is the blueprint for all cell functions, and alterations in the way the cell reads this blueprint is often the first step towards a cell becoming cancerous. In 2005, it was discovered that the majority of prostate cancer cells harbor genetic rearrangements in their chromosomes, the most common of which is a gene fusion that combines the regulatory region of the TMPRSS2 gene to the coding region of the ERG transcription factor. However, little is known about the functional role of this fusion product. Dr. David Rickman at Cornell University, with the support of his laboratory members and an FY08 PCRP New Investigator Award, has taken a variety of approaches to better understand the role of ERG and gene fusions in promoting aggressive prostate cancer. Using a new technology called Hi-C to analyze the 3D structure of chromosomes, Dr. Rickman made the key discovery that the abnormal protein derived from the TMPRSS2-ERG fusion causes significant changes in chromosome structure. These structural changes increase the accessibility of genes that are usually hidden within the chromosome, some of which are relevant to the development of more aggressive prostate cancer. Dr. Rickman's work emphasizes the important role that an oncogenic transcription factor such as TMPRSS2-ERG can play on chromatin structure, and that understanding the role of gene fusions in prostate cancer development and progression will be complex and likely involve many more genes than originally anticipated. Dr. Rickman continues to investigate the mechanisms underlying how ERG reorganizes the genome, and he hopes that additional findings will lead to better biomarker development, targeted therapeutics, and overall better management of high-risk prostate cancer patients.



Hi-C data matrices showing gene-gene interaction correlation on chromosome 6 from prostate cells with and without ERG over-expression. Yellow shows high degree of interaction correlation: green is low. The boxed area shows dramatic increase in the interactions between distant regions on chromosome 6 in ERG cells.



Circos plot of Hi-C data depicting all chromosomes. Orange lines show enriched interactions and blue lines show reduced interactions in cells where ERG is over-expressed.



"It is an honor and a pleasure to serve as a programmatic reviewer for the PCRP. I am delighted by the unfailingly objective and supportive discussions by our panel that consistently result in the selection of not only the most outstanding research applications, but also those that are most relevant to the PCRP's goals and objectives. This is an exemplary group of physicians, scientists and advocates, all of whom take the role very seriously. I am equally pleased by the empathy and understanding our committee shows for those outstanding applications that unfortunately fall outside the target funding areas. I look forward to continuing my service to the program."

Chris Albanese, Ph.D., Georgetown University Medical Center, Lombardi Cancer Center



New Insights into Familial Prostate Cancer

Yang Liu, Ph.D., University of Michigan

To understand the genetic factors that contribute to the risk of developing prostate cancer, many studies have investigated prostate cancer incidence within families. Interestingly, it has been shown that familial prostate cancer incidence is greater between siblings than between a father and son, although the genetic basis for this is largely unknown. At the University of Michigan, Dr. Yang Liu is studying the X chromosome with the intent to identify genes that correlate with familial, or heritable, prostate cancer. Since the X chromosome is inherited from the maternal side, brothers can share X chromosomes, but fathers and sons do not, possibly explaining the sibling correlation. With the support of an FY08 Idea Development Award, Dr. Liu and his laboratory characterized FOXP3, an X-linked gene that suppresses prostate cancer and is inactivated in cancer cells. This finding propelled Dr. Liu to conduct a systematic investigation including family-based association studies to identify variants of genes previously implicated in prostate cancer risk. In collaboration with Dr. Kathleen Cooney, Dr. Liu's research group analyzed approximately 500 families, and discovered a common variant in the X chromosome that was associated with the risk of prostate cancer. As his research continues, Dr. Liu plans to continue examining rare variants of FOXP3, and to demonstrate its role in prostate cancer development using an animal model. This research will not only help to solve a key mystery in the genetics of prostate cancer, but also may reveal important markers for identification of high-risk populations, and will hopefully present valuable targets for development of new therapeutics.



Methylation Biomarkers for Diagnosis and Risk Stratification of Prostate Cancer

Krishna Vanaja Donkena, Ph.D., Mayo Clinic, Rochester

Alterations to DNA methylation, which serves as the “on-off” switches of genes, occur early in the development of prostate cancer and could be used as biomarkers to detect the disease earlier than current approaches. When this process of DNA methylation turns off the activity of tumor suppressor genes, cancer develops. Profiles of these DNA methylation biomarkers can also predict if the cancer is going to recur and whether the recurrence will remain localized to the prostate or, instead, spread to other organs.

With support from an FY08 New Investigator Award, Dr. Krishna Donkena and her colleagues at the Mayo Clinic in Rochester, Minnesota have been able to identify the methylation changes that occur across the entire human genome in prostate cancer tissues. They analyzed the methylation status of 14,495 genes from 238 prostate cancer patients. The patients included men who remained cancer-free after treatment, those who had a localized tumor recurrence, and those whose cancer had spread. They found distinct methylation changes that corresponded to whether a patient had a slow-growing tumor known as an indolent tumor, or a more aggressive one. These DNA methylation changes can be used as biomarkers not only for detection of prostate cancer, but also to distinguish between patients with varying levels of recurrence risk, both of which would represent significant improvements over the widely used PSA (prostate-specific antigen) test. The ability to know whether a patient's prostate cancer is aggressive or indolent would be an enormous advancement in prostate cancer management as patients with indolent tumors would avoid unnecessary treatment, and those with aggressive tumors would be treated earlier and more effectively.



Peter Carroll, M.D., M.P.H.



Matthew Cooperberg, M.D., M.P.H.



June Chan, Sc.D.

Predicting Prostate Cancer Progression at Time of Diagnosis

Peter Carroll, M.D., M.P.H., University of California, San Francisco

It has become clear that improved biomarkers are key to helping clinicians and patients make better treatment decisions. The identification of unique molecular characteristics of prostate cancer cells, and understanding the clinical significance of those characteristics, will influence decisions about the timing and intensity of treatment, or whether treatment is even necessary at all. To date, many novel prostate cancer biomarkers have been proposed, but very few have been confirmed to contribute independent information beyond currently available clinical data, and virtually none have been subject to rigorous external validation, making them an unreliable predictor for treatment decision-making. Dr. Peter Carroll's group at the University of California, San Francisco has been working for a number of years on how to improve risk stratification of prostate cancer at the time of diagnosis, and they had reached a point where they believed there was no further information that could be gained from standard clinical variables such as PSA levels and tumor grade. Instead they have been seeking to understand the genetics and other determinants of prostate cancer behavior, with the goal of developing new blood and tissue tests, imaging studies, and other risk stratification tools for men diagnosed with the disease. Thus, Dr. Carroll felt the PCRP Impact Award mechanism, newly created in FY10, was the perfect vehicle for supporting advancement of this type of research project, which is in line with the Impact Award's goal of making a major impact on reducing the over-treatment of primary prostate cancer. As a recipient of one of the first Impact Awards, Dr. Carroll and his collaborators have started working to identify previously described, promising biomarkers in blood, urine, and tissue, and to validate these in multi-institutional cohorts of men with clinically low-risk prostate cancer. If the molecular markers are validated, the next steps will be prospective studies in the clinic to see how this new information actually influences physician recommendations and patient choices. Eventually, the molecular information will be integrated with other data about clinical tumor risk, patient age and overall health, diet and lifestyle factors, and other factors to help patients make well-informed decisions with which they can be comfortable over the long-term. Through his collaborations with the University of Washington, the other members of the Prostate Active Surveillance Study sponsored by the Canary Foundation, and industry partners, Dr. Carroll plans to further leverage his support from the PCRP to achieve rapid progress in risk stratification and treatment decision-making for men with prostate cancer.

"The PCRP Impact Award mechanism was a perfect—and unique—mechanism for this research proposal. Much effort is typically directed to basic research and development of novel candidate biomarkers. Funding for validation studies, which are at least as important for determining ultimate real-world effectiveness and utility of the markers, tends to be much more scarce. We are very grateful for this support and opportunity."

Peter Carroll, M.D., M.P.H.

COMBINED TREATMENT MODALITIES FOR PROSTATE CANCER

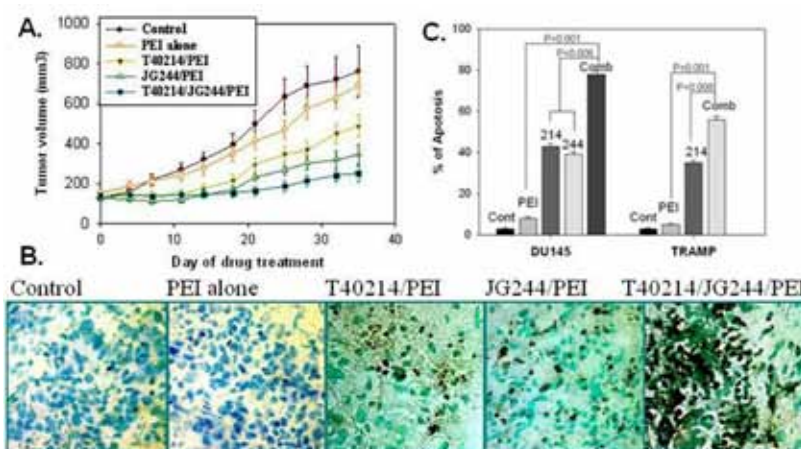
In the absence of effective treatment strategies to assure long-term survival of patients with metastatic disease, new therapeutic approaches are needed. Despite the specificity and potency of individual cytotoxic anticancer drugs, increasing evidence indicates they are not sufficient to cure prostate cancer. We now know that optimal clinical management of this disease requires a combination of synergizing therapeutic strategies incorporating chemotherapy, radiotherapy, vaccines, antibodies, and other modalities. The PCRP not only supports research in these areas but encourages the exploration and development of novel agents such as those found in plants and vegetables so that their therapeutic efficacy can be evaluated.



Development of a Combination Therapy for Prostate Cancer by Targeting Stat3 and HIF-1alpha

Naijie Jing, Ph.D., Baylor College of Medicine

Prostate cancer has been well characterized as a highly complex disease with numerous contributing factors that may respond to different therapeutic approaches. As a result, it may be unlikely that using just one type of therapy to treat men with advanced prostate cancer will be completely effective. To increase patient survival, clinicians attack the cancer from multiple angles, attempting to disrupt more than one pathway crucial for the prostate cancer cells' survival. At the Baylor College of Medicine, Dr. Naijie Jing wanted to investigate the possibility of targeting two different pathways that have both been implicated in prostate cancer cell survival: Stat3 and HIF-1-alpha. Stat3 has been an attractive target for cancer therapy since it functions to control the expression of many different genes, including those involved in preventing cell death, angiogenesis, and anti-tumor immune responses; however, no Stat3 inhibitor drugs are on the market currently. More recently, the HIF-1-alpha factor has also been linked to prostate cancer cell survival. Reduced oxygen (hypoxia) and genetic alterations within the tumor lead to increased levels of HIF-1-alpha that associate with a poor prognosis and treatment failure, also making HIF-1-alpha a potentially good target for cancer therapeutics. With support from an FY09 Idea Development Award, Dr. Jing set out to test the effects of treating metastatic prostate cancer cells with a combination of T40214 (Stat3 inhibitor) and JG244 (HIF-1-alpha inhibitor). In comparison to treatment with either drug alone, the combined treatment greatly increased prostate cancer cell death in animal models. These results not only demonstrate the potentially powerful effect of combined therapy of these two agents, but they also suggest that HIF-1-alpha inhibitors could reduce the hypoxia-induced drug resistance to other therapies (such as T40214), ultimately enhancing drug efficacy and patient survival.



(A) Plot of tumor volume vs. day of drug treatment in DU145 human prostate tumors. The single treatments are T40214 ($P<0.05$) and JG244 ($P<0.01$). T40214/JG244/PEI is a combined treatment ($p<0.002$). (B) The TUNEL stain generates dark brown precipitates in the presence of cleaved DNA fragments, which correspond to apoptotic cells. (C) Plots of the percentage of apoptotic cells within prostate tumor xenografts assessed by TUNEL staining. Cont: control; Comb: combination treatment. The data showed that combined treatment dramatically induced tumor cell apoptosis in prostate tumors.



Increased Chemoprevention through the Combined Use of Green Tea and the Natural Methylation Inhibitor Quercetin in Prostate Cancer

Piwen Wang, Ph.D., University of California, Los Angeles

Natural therapeutic treatment options, or nutraceuticals, are a topic of great interest for cancer patients. Dr. Piwen Wang, an FY09 Prostate Cancer Training Award recipient as a postdoctoral fellow at the University of California at Los Angeles, and his mentor Dr. Susanne Henning investigated the combinatorial treatment of green tea with quercetin, a natural compound found in apples, broccoli, onions, and other dietary sources. Dr. Wang hypothesized that quercetin could enhance the anti-cancer activity of green tea by inhibiting an enzyme, catechol-O-methyltransferase, that typically methylates the active compound of green tea, epigallocatechin gallate (EGCG) to less active metabolites in the body. Expanding on previous results from cell culture studies, Dr. Wang administered brewed green tea and/or a quercetin-supplemented diet to immunodeficient (SCID) mice containing prostate xenograft tumors. As predicted, the combination treatment of green tea plus quercetin provided a significant increase in tumor growth inhibition after 6 weeks (45%) compared to quercetin alone (16%) or green tea alone (21%), and this synergistic effect correlated with increased absorption and decreased methylation of EGCG in the tumor tissues. As Dr. Wang continues in his prostate cancer research career, he plans to confirm these results in human prostate tissue samples, which if successful would further support the possibility of combined green tea and quercetin therapy as an improved option for the prevention of or adjunct treatment for prostate cancer. Finding a similar effect in human samples would be especially exciting given that a quercetin supplement is already on the market for the treatment of prostatitis, and thus relevant treatment options might become quickly available for cancer patients.



Gerald (G.B.) Hammond, Ph.D.

Amazonian Plants with Selective Anticancer Properties

Gerald (G.B.) Hammond, Ph.D., University of Louisville

Ethnomedicinal chemistry, or the use of plants and their constituents for medicinal purposes, has been used culturally for thousands of years. However, the practice of identifying potentially new therapeutic compounds from plants is regarded as old-fashioned. Dr. Gerald "G.B." Hammond of the University of Louisville received support from the PCRP through an FY06 Idea Development Award to screen compounds isolated from plant species found in the Amazonian forest – one of the most biodiverse regions in the world – for natural products that demonstrate potent and selective anti-proliferative activities for treating prostate cancer cells. Starting with almost forty plant species, Dr. Hammond and his colleagues analyzed 29 different compounds, and found that approximately 13 of these had significant activities. Dr. Hammond noted that "it is a common belief among the scientific community at large that ethnobotany-based drug discovery is inefficient compared with advances in other fields, akin to a 'fishing expedition.' What is less known is the fact that of all ethnomedical reports on about 14,300 plant species, there has been no compound isolated and no biological work conducted for 8,387 (58.6%) of them! Yet of all those plant-derived products currently used as prescription drugs, 72% are used in a manner which parallels their ethnomedicinal use. Thus, there is abundant opportunity for the discovery of new anticancer agents from natural sources. Other funding agencies considered our project a fishing expedition, but the results from this research, supported by PCRP funding, proved them wrong." Dr. Hammond has a patent application submitted for his work, and is currently conducting further tests on the most promising compounds.



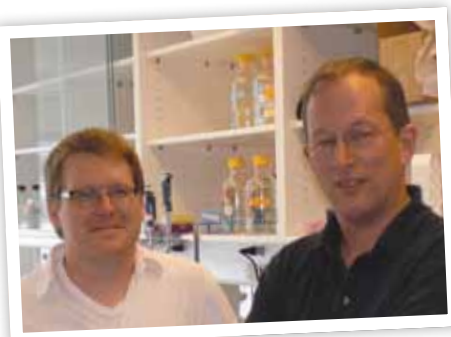
Abraham Vaisberg, Ph.D.



Paula Bates, Ph.D.

HARNESSING THE BODY'S IMMUNE SYSTEM TO FIGHT CANCER: IMMUNOTHERAPY

Steady progress in understanding interaction between immune cells and the tumor microenvironment in advanced metastatic disease, and the use of dendritic cells in stimulating patients' T-cells to recognize and attack advanced prostate cancer cells, have led to the development of immunomodulatory drugs. Recent FDA approval of sipuleucel-T (PROVENGE®) for treating patients with asymptomatic metastatic prostate cancer has given credence to scientists who have long struggled to exploit cellular immune-effector mechanisms, the host immune system, and tumor-specific antibodies to develop an immunotherapy-based approach for the treatment of prostate cancer. PCRP-funded investigators are making breakthroughs in this exciting area of research and are poised to deliver new therapies for validation in clinical trials.



Darrell Irvine, Ph.D., and Karl Wittrup, Ph.D.



Jianzhu Chen, Ph.D.

T-Pharmacytes for Prostate Cancer Immunotherapy

Darrell Irvine, Ph.D., Karl Wittrup, Ph.D., and Jianzhu Chen, Ph.D., Massachusetts Institute of Technology

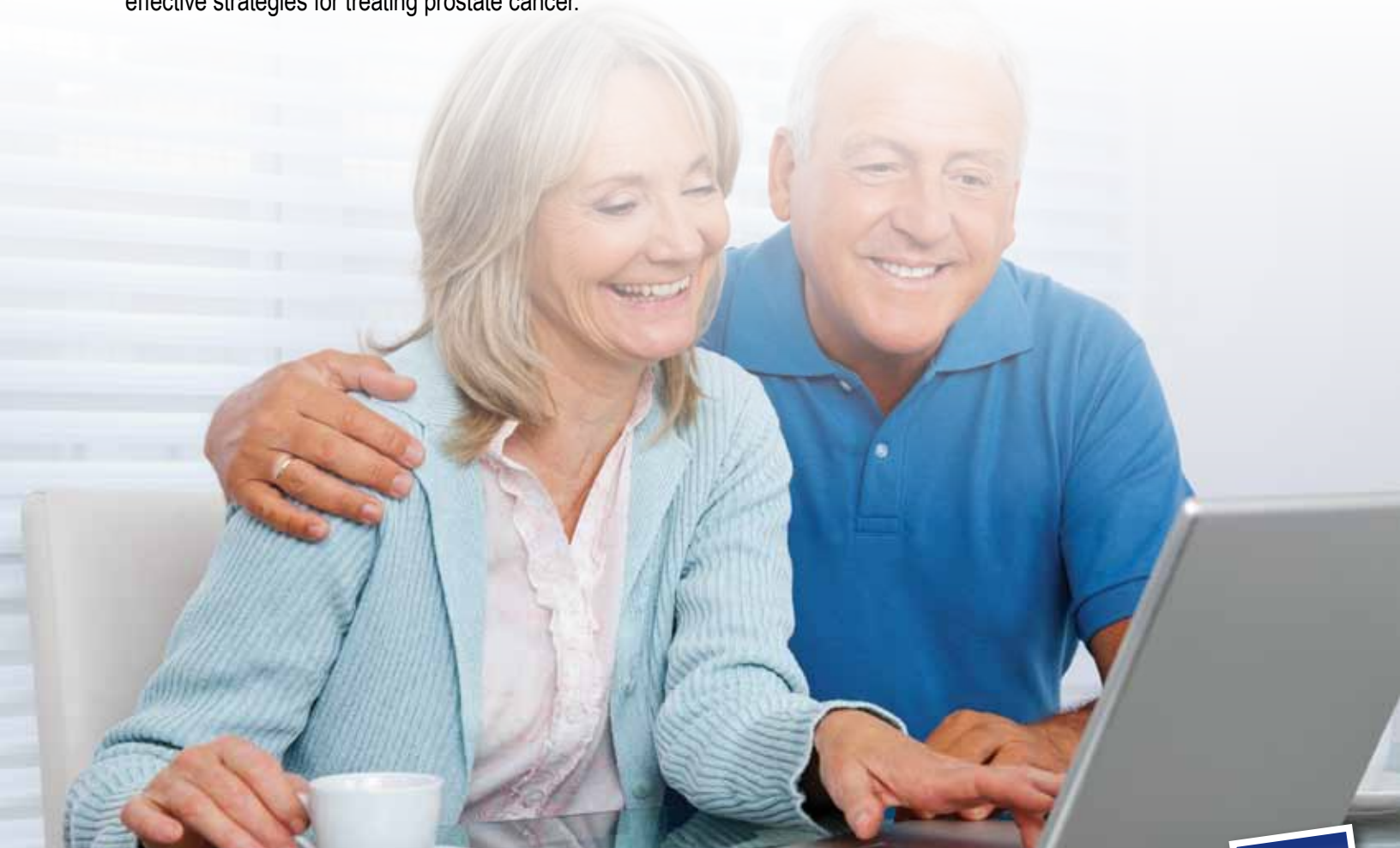
Standard therapies for prostate cancer, such as chemotherapy and radiation, are often toxic to the body and cause many undesirable side effects. One alternative approach under investigation is to attack cancer cells by activating the patient's immune system through immunotherapy. Since prostate tumor cells are molecularly distinct from normal host tissues, the immune system can distinguish healthy and tumor tissue, making the therapy more targeted and less likely to induce side effects. A particularly promising immunotherapy approach, called Adoptive Cell Therapy, works by treating patients with their own (autologous) T-cells that have been activated and expanded in tissue culture so that they can better attack the tumor. However, challenges still exist with this type of therapy, including the loss of T-cells' cytotoxic tumor-killing activity and their ability to produce cytokines. Using a team science approach through an FY09 PCRP Synergistic Idea Development Award, Massachusetts Institute of Technology investigators Dr. Darrell Irvine, Dr. Karl Wittrup, and Dr. Jianzhu Chen hypothesized that they could overcome some of these challenges by providing needed cytokine signals specifically to transferred T-cells. Using nanotechnology, they created 'T-Pharmacytes,' or small particles with cytokine proteins that would attach to the surface of T-cells and cause increased activation of the therapeutic immune cells. While these studies are still in the preclinical testing phase, the results, if successful, could be adopted by ongoing immunotherapy clinical trials and possibly reach the broader patient population in a relatively short time span.



ICOS-Expressing T Cells as Mediators of Antitumor Immune Responses

Padmanee Sharma, M.D., Ph.D., University of Texas M. D. Anderson Cancer Center

Immunotherapy for prostate cancer is rapidly evolving with the advent of PROVENGE® and several alternative treatment strategies that are currently in clinical trials. One approach that is showing some success involves targeting a T-cell surface protein called cytotoxic lymphocyte antigen-4 (CTLA-4). This protein normally acts to inhibit the T-cell-mediated immune response, which can suppress the body's immune response to the presence of cancer. It has been shown that blockade of the inhibitory signals mediated by CTLA-4 can lead to enhanced immune responses and subsequent rejection of tumors in animal models, making CTLA-4 an attractive target for immunotherapy in prostate cancer treatment. In prostate cancer patients, a monoclonal antibody against CTLA-4 has been found to elicit positive responses, including complete regression of disease in a subset of patients. Since the reasons that more patients do not respond to this therapy are unknown, Dr. Padmanee Sharma and her colleagues at the M.D. Anderson Cancer Center are investigating biologic mechanisms that lead to anti-tumor responses. They have observed from a recent clinical trial that patients' T-cells had high levels of the inducible costimulator (ICOS) molecule after receiving treatment with anti-CTLA-4 antibody. Consequently, with support from an FY09 Idea Development Award, Dr. Sharma investigated the role of ICOS in mouse models and discovered that ICOS plays an important role in mediating optimal anti-tumor responses after treatment with anti-CTLA-4, suggesting that ICOS can be targeted in order to improve anti-CTLA-4 therapy for patients. Currently, anti-CTLA-4 is being tested in two Phase III clinical trials in patients with prostate cancer. As Dr. Sharma continues to investigate whether combination therapy consisting of anti-CTLA-4 plus targeting of ICOS can improve tumor rejection in mouse models, she is hopeful that her data will guide future development of clinical trials with even more effective strategies for treating prostate cancer.



PCRP FY11 and FY12 Investments

In FY11, the program offered 11 award mechanisms designed to support basic, translational, and clinical research. Additionally, the program supported the training of promising new investigators. While a majority of the award mechanisms focused on high-impact and innovative research, the program for the second consecutive year brought into sharp focus the continuing problem of overtreatment of primary prostate cancer by offering an award mechanism with directed emphasis on this issue (Impact Award). Applications received by the PCRP in FY11 numbered 1,298 following pre-application screening, and the PCRP Integration Panel recommended 173 awards for funding.

In FY12, based on the significant investment the program had made over the past 15 years in discovery-driven research, awards were made to emphasize translational research. Twelve award mechanisms included support for qualifying and validating biomarkers for clinical use, clinical trials that study innovative therapies and therapeutic approaches, translation of clinically impactful therapeutic agents, and large-scale, team-based translational and clinical research to transform clinical practice, in addition to continued support for new discoveries, training for early-career investigators positioned to continue the gains made in recent years, and targeted efforts to understand and resolve disparities in prostate cancer incidence, morbidity, and mortality.

Table 1. PCRP Investment Summary for FY11 and FY12





Focus and Award Mechanisms	FY11 Applications Received	FY11 Awards	FY12 Applications Received	FY12 Awards
Impact Research				
Biomarker Development Award	n/a	n/a	13	0
Clinical Exploration Award	n/a	n/a	18	1
Clinical Trial Award	16	0	n/a	n/a
Health Disparity Research Award	41	5	43	6
Impact Award	20	2	n/a	n/a
Laboratory-Clinical Transition Award	23	1	23	2
Population-Based Research Award	11	1	n/a	n/a
Transformative Impact Award	n/a	n/a	10	3
Innovative Research				
Exploration-Hypothesis Development Award	365	38	387	31
Idea Development Award	516	62	338	32
Synergistic Idea Development Award	141	21	144	13
Training/Recruitment				
Collaborative Undergraduate HBCU Student Summer Training Program	10	6	9	5
Health Disparity Training Award	11	2	n/a	n/a
Physician Research Training Award	21	4	20	5
Postdoctoral Training Award	123	31	122	31
Total	1,298	173	1,127	129

n/a – not offered in that fiscal year

The Vision for FY13

In FY13, the PCRP received \$80M in congressional appropriations. The PCRP Integration Panel developed an investment strategy for FY13 that would continue to enhance the program's emphasis on translational and clinical research, innovation, health disparity, and training. In addition, the strategic recommendation was made to continue key support for research resources by offering new funding opportunities with the Clinical Consortium Award and the Prostate Cancer Pathology Resource Network Award, both of which are designed to increase the pace of research by respectively leveraging resources in the conduct of prostate cancer clinical trials or providing to the research community high-quality, well-annotated biospecimens that are in limited supply but much needed to advance improvements for patients. The program also renewed its support for population science to identify and investigate key determinants that affect prostate cancer in specific populations of men. The following thirteen award mechanisms were carefully selected to maximize the impact of the FY13 PCRP investment toward eliminating death from prostate cancer and enhancing the well-being of men experiencing the impact of the disease:

Table 2. PCRP FY13 Vision (Award Mechanisms)

Focus	Award Mechanism
 Impact Research	Biomarker Development Award: Supports high impact research aimed at qualifying and/or validating prostate cancer biomarkers for rapid transfer to clinical practice.
	Health Disparity Research Award: Supports high-impact approaches to prostate cancer health disparity research that represent new ideas. Additional funding available for the <i>Qualified Collaborator</i> and/or <i>Nested Traineeship Options</i> .
	Laboratory-Clinical Transition Award: Provides funding for product-driven preclinical studies of promising lead agents (including devices) that may revolutionize prostate cancer clinical care.
	Population Science Impact Award: Supports high-impact, population science approaches to prostate cancer research with emphasis on biomarkers, especially those relevant to aggressive disease; genetics/genomics; therapy and predictors of response or resistance; and survivorship and palliative care.
	Transformative Impact Award: Supports near-term research projects specifically designed to have a transformative impact on prostate cancer management.
 Innovative Research	Exploration-Hypothesis Development Award: Supports highly innovative, untested, potentially groundbreaking concepts in prostate cancer.
	Idea Development Award: Supports new ideas that represent innovative, high-risk/high-gain approaches to prostate cancer research. The <i>New Investigator Option</i> provides additional emphasis for investigators in the early stages of, or developing, independent prostate cancer research careers.
	Synergistic Idea Development Award: Supports new or existing partnerships between two or three independent investigators to address a central question in prostate cancer through synergistic and innovative approaches that may include high risk with potential for significant impact.
 Training/Recruitment	Collaborative Undergraduate HBCU Student Summer Training Program Award: Supports new or existing summer training programs for undergraduate HBCU students at host institutions with thriving prostate cancer research programs.
	Physician Research Training Award: Provides support for physicians with clinical duties to pursue training for careers at the forefront of prostate cancer research.
	Postdoctoral Training Award: Provides support for recent doctoral graduates to pursue postdoctoral training in prostate cancer research.
 Research Resources	Clinical Consortium Award: Provides the support to develop and enhance collaborations and resources necessary for a network of organizations to rapidly execute Phase II or Phase II-linked Phase I (Phase I/II) prostate cancer clinical trials.
	Prostate Cancer Pathology Resource Network Award: Provides infrastructure support for the development and maintenance of a prostate cancer biorepository through a collaborative network across multiple institutions that will facilitate the collection, processing, annotation, storage, and distribution of high-quality human prostate cancer biospecimens, especially those in limited supply.



For more information, visit

<http://cdmrp.army.mil>

or contact us at:

usarmy.detrick.medcom-cdmrp.mbx.cdmrp-public-affairs@mail.mil

(301) 619-7071

